

Appendix 4 – Amended Claims

Cancel claim 35 without prejudice.

36. (Amended) The [composition] method of [claim 35,] 50, 59, 64, 66, 68 or 71, wherein the at least one proton pump inhibitor compound is a benzimidazole, a quinoline, a pyrimidine, a thiadiazole, a sulfinylnicotinamide, a thienoimidazole, or a imidazopyridine.

37. (Twice Amended) The [compound] method of claim 36, wherein the benzimidazole is omeprazole, lansoprazole, pantoprazole, rabeprazole, leminoprazole, timoprazole, tenatoprazole, disulprazole, esomeprazole, 2-(2-benzimidazolyl)-pyridine, a tricyclic imidazole, a thienopyridine benzimidazole, a fluoroalkoxy substituted benzimidazole, a dialkoxo benzimidazole, a N-substituted 2-(pyridylalkenesulfinyl) benzimidazole, a cycloheptenepyrindine, a 5-pyrrolyl-2-pyridylmethylsulfinyl benzimidazole, a alkylsulfinyl benzimidazole, a fluoro-pyridylmethylsulfinyl benzimidazole, an imidazo(4,5-b)pyridine, RO 18-5362 or IY 81149; wherein the quinoline is a 4-amino-3-carbonyl quinoline, a 4-amino-3-acylnaphthyride, a 4-aminoquinoline, a 4-amino-3-acylquinoline or a 3-butyryl-4-(2-methylphenylamino)-8-(2-hydroxyethoxy)quinoline; wherein the pyrimidine is a quinazoline, a tetrahydroisoquinolin-2-yl pyrimidine or YH 1885; wherein the thiadiazole is 3-substituted 1,2,4-thiadiazolo(4,5-a) benzimidazole or a 3-substituted imidazo(1,2-d)-thiadiazole; wherein the sulfinylnicotinamide is a 2-sulfinylnicotinamide; wherein the thienoimidazole is a pyridylsulfinylbenzimidazole, a pyridylsulfinyl thienoimidazole, a thienoimidazole-toluidine, a 4,5-dihydrooxazole, a thienoimidazole-toluidine or Hoe-731; wherein the imidazopyridine is a imidazo(1,2-a)pyridine, a pyrrolo(2,3-b)pyridine or a pharmaceutically acceptable salt thereof.

38. (Amended) The [composition] method of claim 37, further comprising administering a pharmaceutically acceptable carrier.

39. (Twice Amended) The [composition] method of [claim 35,] 50, 59, 64, 66, 68 or 71, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is an S-nitrosothiol.

40. (Amended) The [composition] method of claim 39, wherein the S-nitrosothiol is S-nitroso-N-acetylcysteine, S-nitroso-captopril, S-nitroso-N-acetylpenicillamine, S-nitroso-homocysteine, S-nitroso-cysteine or S-nitroso-glutathione.

41. (Amended) The [composition] method of claim 39, wherein the S-nitrosothiol is:

- (i) $\text{HS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{SNO}$;
- (ii) $\text{ONS}(\text{C}(\text{R}_e)(\text{R}_f))_m\text{R}_e$; and
- (iii) $\text{H}_2\text{N}-\text{CH}(\text{CO}_2\text{H})-(\text{CH}_2)_m-\text{C}(\text{O})\text{NH}-\text{CH}(\text{CH}_2\text{SNO})-\text{C}(\text{O})\text{NH}-\text{CH}_2-\text{CO}_2\text{H}$;

wherein m is an integer from 2 to 20; R_e and R_f are each independently a hydrogen, an alkyl, a cycloalkoxy, a halogen, a hydroxy, an hydroxyalkyl, an alkoxyalkyl, an arylheterocyclic ring, an alkylaryl, a cycloalkylalkyl, a heterocyclicalkyl, an alkoxy, a haloalkoxy, an amino, an alkylamino, a dialkylamino, an arylamino, a diarylamino, an alkylarylamino, an alkoxyhaloalkyl, a haloalkoxy, a sulfonic acid, a sulfonic ester, an alkylsulfonic acid, an arylsulfonic acid, an arylalkoxy, an alkylthio, an arylthio, a cycloalkylthio, a cycloalkenyl, a cyano, an aminoalkyl, an aminoaryl, an aryl, an arylalkyl, an alkylaryl, a carboxamido, an alkylcarboxamido, an arylcarboxamido, an amidyl, a carboxyl, a carbamoyl, an alkylcarboxylic acid, an arylcarboxylic acid, an alkylcarbonyl, an arylcarbonyl, an ester, a carboxylic ester, an alkylcarboxylic ester, an arylcarboxylic ester, a haloalkoxy, a sulfonamido, an alkylsulfonamido, an arylsulfonamido, a sulfonic ester, a urea, a phosphoryl, a nitro, -T-Q, or $(\text{C}(\text{R}_e)(\text{R}_f))_k-\text{T}-\text{Q}$, or R_e and R_f taken together with the carbons to which they are attached form a carbonyl, a methanthial, a heterocyclic ring, a cycloalkyl group or a bridged cycloalkyl group; Q is -NO or -NO₂; and T is independently a covalent bond, a carbonyl, an oxygen, -S(O)_o- or -N(R_a)R_i-, wherein o is an integer from 0 to 2, R_a is a lone pair of electrons, a hydrogen or an alkyl group; R_i is a hydrogen, an alkyl, an aryl, an alkylcarboxylic acid, an aryl carboxylic acid, an alkylcarboxylic ester, an arylcarboxylic ester, an alkylcarboxamido, an arylcarboxamido, an alkylaryl, an alkylsulfinyl, an alkylsulfonyl, an arylsulfinyl, an arylsulfonyl, a sulfonamido, a carboxamido, a carboxylic ester, an amino alkyl, an amino aryl, -CH₂-C(T-Q)(R_e)(R_f), or -(N₂O₂-)•M⁺, wherein M⁺ is an organic or inorganic cation; with the proviso that when R_i is -CH₂-C(T-Q)(R_e)(R_f) or -(N₂O₂-)•M⁺; then "-T-Q" can be a hydrogen, an alkyl group, an alkoxyalkyl group, an aminoalkyl group, a hydroxy group or an aryl group.

42. (Twice Amended) The [composition] method of [claim 35,] 50, 59, 64, 66, 68 or 71, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is L-arginine, L-homoarginine, N-hydroxy-L-arginine, nitrosated L-arginine, nitrosylated L-arginine, nitrosated

N-hydroxy-L-arginine, nitrosylated N-hydroxy-L-arginine, citrulline, ornithine, glutamine, lysine, polypeptides comprising at least one of these amino acids or inhibitors of the enzyme arginase.

43. (Twice Amended) The [composition] method of [claim 35,] 50, 59, 64, 66, 68 or 71, wherein the compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase is:

- (i) a compound that comprises at least one ON-O-, ON-N- or ON-C- group;
- (ii) a compound that comprises at least one O₂N-O-, O₂N-N-, O₂N-S- or -O₂N-C- group;
- (iii) a N-oxo-N-nitrosoamine having the formula: R¹R²-N(O-M⁺)-NO, wherein R¹ and R² are each independently a polypeptide, an amino acid, a sugar, an oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted hydrocarbon, or a heterocyclic group, and M⁺ is an organic or inorganic cation.

44. (Amended) The [composition] method of claim 43, wherein the compound comprising at least one ON-O-, ON-N- or ON-C- group is an ON-O-polypeptide, an ON-N-polypeptide, an ON-C-polypeptide, an ON-O-amino acid, an ON-N-amino acid, an ON-C-amino acid, an ON-O-sugar, an ON-N-sugar, an ON-C-sugar, an ON-O-oligonucleotide, an ON-N-oligonucleotide, an ON-C-oligonucleotide, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-O-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-N-hydrocarbon, a straight or branched, saturated or unsaturated, substituted or unsubstituted, aliphatic or aromatic ON-C-hydrocarbon, an ON-O-heterocyclic compound, an ON-N-heterocyclic compound or a ON-C-heterocyclic compound.

45. (Amended) The [composition] method of claim 43, wherein compound comprising at least one O₂N-O-, O₂N-N-, O₂N-S- or O₂N-C- group is an O₂N-O-polypeptide, an O₂N-N-polypeptide, an O₂N-S-polypeptide, an O₂N-C-polypeptide, an O₂N-O-amino acid, O₂N-N-amino acid, O₂N-S-amino acid, an O₂N-C-amino acid, an O₂N-O-sugar, an O₂N-N-sugar, O₂N-S-sugar, an O₂N-C-sugar, an O₂N-O-oligonucleotide, an O₂N-N-oligonucleotide, an O₂N-S-oligonucleotide, an O₂N-C-oligonucleotide, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-O-hydrocarbon, a straight or branched,

saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-N-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-S-hydrocarbon, a straight or branched, saturated or unsaturated, aliphatic or aromatic, substituted or unsubstituted O₂N-C-hydrocarbon, an O₂N-O-heterocyclic compound, an O₂N-N-heterocyclic compound, an O₂N-S-heterocyclic compound or an O₂N-C-heterocyclic compound.

Cancel claim 46-49 without prejudice.

50. (Amended) A method for improving the gastroprotective properties, the anti-*Helicobacter pylori* properties, or the antacid properties of a proton pump inhibitor comprising administering to a patient in need thereof a therapeutically effective amount of at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. [the composition of claim 35.]

Cancel claims 52-55 without prejudice.

59. (Twice Amended) A method for preventing or treating a gastrointestinal disorder, wherein the gastrointestinal disorder is Crohn's disease, ulcerative colitis, a peptic ulcer, a stress ulcer, a bleeding peptic ulcer, a duodenal ulcer, infectious enteritis, colitis, diverticulitis, gastric hyperacidity, dyspepsia, gastroparesis, Zollinger-Ellison syndrome, gastroesophageal reflux disease, a *Helicobacter Pylori* associated disease, short-bowel syndrome, or a hypersecretory state associated with systemic mastocytosis or basophilic leukemia and hyperhistaminemia; for facilitating ulcer healing, or for decreasing the recurrence of an ulcer in a patient in need thereof comprising administering to the patient a therapeutically effective amount of at least one proton pump inhibitor or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Cancel claim 61, without prejudice.

64. (Amended) A method for improving the gastroprotective properties, the anti-*Helicobacter* properties or the antacid properties of a proton pump inhibitor compound comprising administering to a patient in need thereof a therapeutically effective amount of at

least one [a] bismuth complex of at least one proton pump inhibitor compound and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase. [comprising at least one composition of claim 35.]

68. (Twice Amended) A method for treating an infection caused by *Helicobacter pylori* comprising administering to a patient in need thereof a therapeutically effective amount of at least one acid degradable antibacterial compound, at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase.

Cancel claims 76-78, without prejudice.

79. (New) The method of claim 50, 59, 64, 66, 68 or 71, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered separately.

80. (New) The method of claim 50, 59, 64, 66, 68 or 71, wherein the at least one proton pump inhibitor compound or the pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered together in the form of a composition.

81. (New) The method of claim 50, 59, 64, 66, 68 or 71, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered orally, buccally, topically, by injection, by inhalation, or by transdermal application.

82. (New) The method of claim 81, wherein the at least one proton pump inhibitor compound or a pharmaceutically acceptable salt thereof, and the at least one compound that donates, transfers or releases nitric oxide, induces the production of endogenous nitric oxide or endothelium-derived relaxing factor, stimulates endogenous synthesis of nitric oxide or is a substrate for nitric oxide synthase are administered orally in a solid dosage form or a liquid dosage form.

83. (New) The method of claim 82, wherein the solid dosage form is a capsule, a tablet, an effervescent tablet, a chewable tablet, a pill, a powder, a sachet, a granule or a gel.

84. (New) The method of claim 82, wherein the liquid dosage form is an emulsion, a solution, a suspension, a syrup, or an elixir.